AVIATION MEDICINE VOLUME 28 NUMBER 1 1984

Pathogenesis, Clinical Course, Complications and treatement of Impaired Glucose Tolerance— Current concepts

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Diagnostic criteria, pathogenesis, natur history, complications and latest trend management of Impaired Glucose Tolerand (IGT) has been described. The justification i favour of the new term IGT in lieu of th older terms, chemical diabetes, latent diabete subclinical diabetes and symptomatic diabet has been highlighted. Patients of IGT exhib an abnormal insulin response to orally intravenously administered glucose. The is increased insulin resistance and redu ed insulin binding. Obesity is associated wi increased insulin resistance and could be co tributory to glucose intolerance in obese cas of IGT. Prospective epidemiological studi of cases of IGT have shown that hyperglycaem is the most important prognostic factor f deterioration to overt diabetes and to an i creased mortality with Coronary Heart Disea (CHD). Increased systolic blood pressure (153 mm Hg) and obesity, defined as Body Ma Index (BMI) > 27 (BMI = weight in kg ÷ Heig in metres^2), are other factors associated wi increased CHD mortality.

Importance of correction of obesity, h been emphasised. The role of fructose a sorbitol in lieu of glucose and sucrose has be discussed. The role of high fibre diet and cont nuous exercise programme in the manageme of cases of IGT has been highlighted.

Introduction

A new term "Impaired Glucose Tolerance" (IG has been legitimised by the World Health Organis sation[1], abrogating to oblivion the older terms l chemical, borderline, subclinical, asymptomatic a latent diabetes. The justification in favour of t terminology is the uncertainty in the natural histo of such a biochemical status and equal possibi of its reversibility to normal glucose tolerance st or progression to overt diabetes. Thus, the term I is more appropriate and is without the psychologi and social stigma for an individual otherwise thou of as being diabetic.

It has been clearly established in recent ye

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that diabetes mellitus and impaired glucose tolerance are genetically[2] and clinically[3,4] heterogenous disorders that share glucose intolerance in common. Heterogeneity implies that different genetic and/or environmental factors can result in similar clinical disorders. It is now apparent that diabetes and glucose intolerance are not diagnostic terms but like anaemia are simply symptom complexes or laboratory abnormalities respectively which can result from a number of distinct etiologic factors[3].

Diagnostic Criteria for IGT[1,4]

Three criteria must be met

(a) the fasting glucose concentration must be below the value that is diagnostic for diabetes,

(b) the glucose concentration two hours after a 75g oral glucose challenge must be between normal and diabetic values; and

(c) a value between ½ hour or 1½ hour OGTT value later, must be unequivocally elevated.

Fasting Value

Venous plasma 140 mg/dl (7.8 mmol/L)
Venous Whole blood 120 mg/dl (6.7 mmol/L)
Capillary Whole blood 120 mg/dl (6.7 mmol/L)

½ hr, 1 hr or 1½ hr OGTT Values

Venous plasma 200 mg/dl (11.1 mmol/L)
Venous Whole blood 180 mg/dl (10.0 mmol/L)
Capillary Whole blood 200 mg/dl (11.1 mmol/L)

2 hr OGTT Value

Venous plasma of between 140 and 200 mg/dl (7.8 and 11.1 mmol/L)
Venous Whole blood of between 120 and 180 mg/dl (6.7 and 10.0 mmol/L)
Capillary Whole blood of between 140 and 200 mg/dl (7.8 and 11.1 mmol/L)

Pathogenesis of IGT

(a) Abnormal Insulin Response

Over the last decade much work has been done[5,6,7] on the insulin response to oral glucose tolerance test (OGTT) and intravenous glucose tolerance test (IVGTT) in case of Non-Insulin Dependent Diabetes Mellitus (NIDDM) and in IGT. Though in NIDDM, an impairment in the early response to OGTT or IVGTT has been consistently observed, the contribution of impaired insulin secretion in the pathogenesis of IGT is less well established. However, Cerasi et al[8] have argued that an impairment in the early insulin response is the earlist detectable lesion in "Chemical Diabetes" or IGT. This defect in the early insulin response leads to early hyperglycaemia which provides a persistent stimulus to the beta cells and is responsible for the normal or elevated plasma insulin level seen during the last phase of OGTT or IVGTT. Although other investigators[5] have published results compatible with this concept. most[6,7] have demonstrated a normal or even increased early insulin release in patients with IGT.

In this respect the conclusions of Efendic et al[9] and Luft et al[10], who have recently reevaluated their data on insulin secretion, are noteworthy. The early as well as the late phase of insulin secretion in IGT patients with an abnormal OGTT but a normal IVGTT were found to be increased in absolute terms. Only in those patients in whom both OGTT and IVGTT were abnormal was the early plasma insulin noted to be impaired. Thus even Luft et al[10] have concluded that the plasma insulin response in patient with IGT may be quite variable and can be increased, normal or decreased.

Fajans et al[11] have recently drawn attention to the heterogeneity of insulin response in normal subjects and in patients with IGT. They have divided patients with comparable degree of glucose intolerance into "low" and "high" responders. Most patients with abnormal OGTT had insulin response greater than normal, none had insulin response less than normal. Most patients with abnormal OGTT were also insulin resistant. A significant correlation existed between insulin response and the degree of insulin resistance. However, when both variables were taken into account the entire population could be divided into two groups. One group was characterised by both normal insulin responsiveness and sensitivity and the other by increased insulin response associated with greater insulin resistance. Most patients with IGT fall into this latter group but

some had glucose intolerance without either an exaggerated insulin response or insulin resistance. These results indicate that true heterogeneity exists in patients with IGT.

(b) Insulin Resistance

Reaven et al[7] have shown that patients with IGT and diabetic patients with fasting hyperglycaemia uniformly demonstrated the presence of insulin resistance. The severity of insulin resistance parallels the degree of carbohydrate intolerance. Examination of the dose response relationship in vivo insulin action in these patients reveals that patients with IGT manifest only decreased sensitivity with a rightward shift of their dose response curve and no alteration in their maximum response. Insulin resistance associated with an abnormal carbohydrate tolerance comprises a spectrum with the least insulin resistant patient having an isolated receptor defect while the more insulin resistant patient exhibits a combined receptor and post receptor defect. Insulin resistance is located in the liver and peripheral tissues, chiefly the muscles. Hepatic resistance to the action of insulin is present in the form of inappropriately high glucose production in the fasting state and deficient glucose uptake following glucose ingestion. Peripheral resistance manifests itself as reduced glucose up take (mostly by muscle) after exposure to exogenous or endogenous insulin and reduce clearance of plasma glucose in fasting state.

(c) Insulin binding

Olefsky et al[12] have shown that insulin binding to monocytes and adipocytes from both IGT and diabetes patients with fasting hyperglycaemia is reduced by approximately 30-40%. He found a positive correlation between decreased insulin binding and severity of insulin resistance in their patients of IGT. They were unable to demonstrate a similar relationship in diabetic patients with fasting hyperglycaemia even though insulin binding was decreased to an extent similar to that in the IGT group. Therefore they concluded that post receptor defect must also contribute to insulin resistance in diabetic patients with fasting hyperglycaemia.

Clinical course of IGT

Prospective epidemiological studies [13,17] have shown that cases of IGT improve[14] or progress to overt diabetes. However, a majority of patients with IGT do not experience deterioration of glucose tolerance with time[14] and this is true irrespective of age.[13] In a 10 year follow up of 241 cases in the Birmingham study[14], 128 (53%) substantially improved their glucose tolerance and 36 (15%) worsened to diabetes. The major predictor of worsening to diabetes is the level of basal blood glucose level [14,15,16,17]. A two hour capillary whole blood concentration of glucose greater than 135 mg/dl has been identified as the point above which the risk of progression to diabetes rises significantly[16]. It is also said that below a two hour whole blood glucose concentration of 198 mg/dl spontaneous remission may occur in some people [14,18]. Though the rate of progression from IGT to diabetes is low, it may be amenable to intervention ; without advice or treatment the rate is about 3% a year[14], with dietary advice[19] this may be reduced to 1.3% yearly and one small study has claimed that with the further addition of tolbutamide[19] the rate may be cut to nil.

It is not definitely known whether patients of IGT who progress to overt diabetes respond to glucose tolerance testing primarily with hypoinsulinaemia or hyperinsulinaemia. Kosaka et al[20] have noted that 12% of 330 patients with equivocal diabetes progressed to diabetes during a mean follow up period of 3.3 years. The insulin response of these patients was normal or even increased as compared to control subjects. However, others[21,22] have emphasised the impaired initial insulin secretory response to glycaemic stimulus in cases of IGT who deteriorate to overt diabetes mellitus.

Body mass index (BMI) = (Weight in kg ÷ Height in metres^2) is a reliable measure of obesity that has been used in epidemiological studies. Obesity has been defined as BMI > 25 in men and > 27 in women. Increased BMI has an adverse prognostic significance in IGT[13,14,23]. In the Bedford study[14], obesity did not predict worsening during the first 5 years but was an independent and significant predictor of worsening during the second 5 year. Family history of diabetes (specially in NIDDM group) may have an adverse prognostic significance[2]. Age, blood pressure, hyperlipidaemia, renal glycosuria and Hb A_1C levels are not of statistical

significance in the progression of IGT to overt diabetic state[11,19].

Complications of IGT

Patients of diabetes mellitus are at increased risk of coronary, peripheral and cerebral arterial diseases[19]. Analysis of eleven prospective studies by the International Collaborative Group[24] has not consistently established a similar extra risk in patients of IGT. However, prospective mortality data from Bedford[15] and two Whitehall studies[16,17] have suggested that subjects with IGT may have an increased risk of Cardiovascular disease. It is now well recognised[25] that minor aberration of glucose tolerance, though asymptomatic, significantly contribute to the large vessel disease. In the first Whitehall study[16] a doubling of CHD mortality was found above the 98th centile of the 2 hour post-glucose blood sugar distribution ($\geq$ 110 mg/dl). This increased mortality was independent of the effects of raised blood pressure and overweight. In the second Whitehall study[17] where 7½ yrs mortality data from the previous study were analysed, CHD mortality increased sharply above the 95th percentile (blood sugar $\geq$ 96 mg/dl). This 2 hour capillary blood sugar value is considerably lower than the proposed lower diagnostic limit for IGT[26] which is 144 mg/dl. However, mean 2 hour blood sugar levels in the Whitehall study[17] were some 20 mg/dl lower than comparative values from most of the International Collaborative study[24]. Thus all cases of IGT have to be followed up so that significantly high CHD mortality may be prevented by "risk factor" intervention[25].

Abnormalities of resting ECG may define at risk groups of patients with IGT who are particularly suitable for dietary or drug intervention[17]. The importance of certain Minnesota-codable ECG findings as independent risk factors for subsequent mortality has been clearly shown in prospective study of nondiabetic population[27]. Nearly all the International Collaborative Group[24] studies showed an increased prevalence of defined ECG abnormality in the IGT range. In the Whitehall IGT group[16, 17] there were significantly increased prevalence of certain specific ECG findings and mortality rate was 3 times higher for those IGT individuals with small Q waves, frequent premature beats and sinus tachycardia[17].

Increased systolic blood pressure ($\geq$ 153mm Hg) and over-weight (BMI > 27) are associated with a higher relative risk of CHD death than normoglycaemic individuals[17].

General and Therapeutic Measures in IGT

The clinical importance of IGT lies in the increased risk of arterial disease and of progression to overt diabetes. The aim, therefore, is to prevent the onset of these complications. With this end in view the role of diet, exercise, prevention of obesity and drugs are discussed.

(a) Correction of Obesity

Eighty percent of patients of IGT are obese. Obesity per se is known to be associated with insulin resistance[3] and high fasting plasma insulin level.[6] Obesity is associated with a higher relative risk of CHD death[17]. Thus, correction of obesity and attainment of ideal body weight should receive highest priority. This can be achieved by hypocalorie diet and exercise.

(b) Carbohydrate Restriction versus Carbohydrate excess

Hypocalorie diet and weight reduction has a small role in patients with normal weights. High carbohydrate diet improves glucose tolerance in healthy nondiabetic control subjects with normal weight by enhancing insulin secretion and tissue sensitivity to insulin[28]. Conversely a low carbohydrate diet has been shown to impair insulin secretion and glucose tolerance in healthy persons[29]. Bruznnell et al[30] treated patients with IGT with a high carbohydrate diet and reported an improvement in OGTT without any change of insulin secretion. High carbohydrate diet, on the other hand may lead to hyperinsulinaemia which would lead to hypertriglyceridaemia. Augmented insulin secretion may accelerate the atherosclerotic process by enhancing the uptake of lipids by arterial smooth muscle cells as well as stimulating their proliferation[31]. In contrast, a low carbohydrate diet has led to improved glucose tolerance even without weight loss[32].

(c) Glycaemic Response to Different Carbohydrates

Carbohydrates can be "complex" or "simple"

Complex carbohydrates are absorbed slowly and lead to a slower rise in blood sugar. On the other hand, simple carbohydrates are more readily absorbed and cause hyperglycaemia. In general, this is true, but there are different starches. Secondly, fructose which is a simple sugar induces a much lower glycaemic response than glucose or sucrose[33]. Fructose is absorbed more slowly than glucose and removed rapidly by the liver. Since tissue uptake of fructose is not dependent on insulin, this would appear as an ideal substitute for glucose in the diet of the patient with IGT or diabetes. Glycaemic response to sorbitol has been noted to be even less than fructose[33]. Although both sorbitol and fructose offer promise as sucrose substitutes, much more information is needed concerning their long term effects before their use merits recommendation.

(d) Role of Fibre

In recent years there has been much interest in the use of high fibre diet[34]. High fibre diet leads to slowing of carbohydrate absorption without impairing total absorption. It lowers fasting plasma glucose level without diminishing the plasma insulin response.

(e) *Beneficial effects of Exercise*

Effect of short term acute exercise is short lived and varies with the type, intensity and duration of exercise performed. Generally it is not advocated in the long term managment of IGT. On the other hand continuous exercise programme is very beneficial. It leads to increased insulin sensitivity and insulin binding to monocytes[35]. Fasting plasma insulin concentration becomes low[36], there is fall in VLDL and triglycerides[37], and there is increase in the activity of insulin sensitive enzyme lipoprotein lipase[38]. Men with IGT can normalise their glucose tolerance by some increase in their weekly physical activity pattern without any change in body weight or lean body mass[39]. Soman et al[39] have examined the effect of long term physical exercise on whole body sensitivity to insulin. They demonstrated that after 6 weeks training programme tissue sensitivity to insulin in 6 young control subjects with normal weight was enhanced by 30% without any change in body weight. It was concluded from this study that the site of improved insulin sensitivity was in the peripheral tissues, primarily the muscles. There was no change in OGTT but insulin level fell significantly. These results clearly indicate th a programme of long term physical exercise signifi cantly augments tissue sensitivity to insulin and the same time reduce the plasma insulin respons to glucose. Recent studies[31] have suggested th hyperinsulinaemia per se may be atherogenic an improvement in tissue sensitivity to insulin may b advantageous even if glucose intolerance remai unchanged.

(f) Therapeutic intervention that affect Insul Resistance

Sulfonylureas are known to increase insul secretion directly and potentiating the stimulato effect of glucose on insulin secretion. On cessatio of long term administration, the basal and stimul ted plasma insulin level return to pretreatment va lues or are even diminished, but the improvemen in glucose tolerance persists. These results strongl suggest that enhancement of insulin sensitivity mu be responsible for sustained improvement[19]. In recent study, the second generation sulfonylure glybanclamide, has been shown to increase th number of insulin receptors[40].

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